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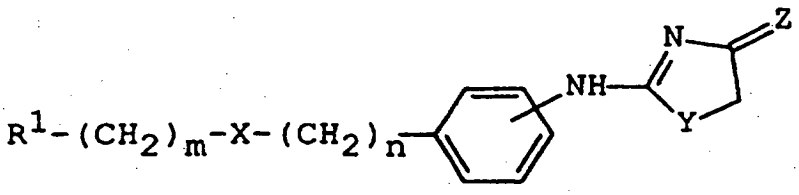
(54) Title: AMIDINE DERIVATIVES



(I)

(57) Abstract

A compound of formula (I), wherein R^1 is heterocyclic group, X is $(CH_2)_a$ in which a is 0 or 1, O or S, Y is CH_2, O, S or N-R^2 in which R^2 is hydrogen or lower alkyl, Z is O or H_2, and m and n are each 0 or 1, and pharmaceutically acceptable salts thereof, which is useful as a medicament for prophylactic and therapeutic treatment of NOS-mediated diseases.

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DESCRIPTION

AMIDINE DERIVATIVES

TECHNICAL FIELD :

This invention relates to amidine derivatives. More particularly, this invention relates to amidine derivatives and pharmaceutically acceptable salts thereof which have pharmacological activities, processes for preparation thereof, a pharmaceutical composition comprising the same and a use of the same.

Accordingly, one object of this invention is to provide the new and useful amidine derivatives and pharmaceutically acceptable salts thereof which possess a strong inhibitory activity on the production of nitric oxide.

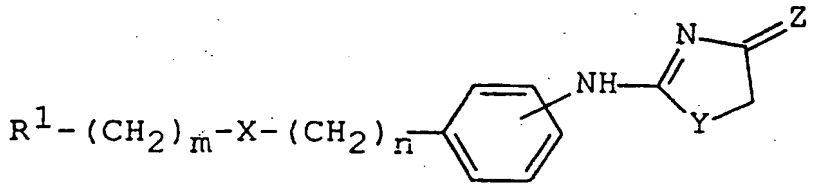
Another object of this invention is to provide process for preparation of the amidine derivatives and salts thereof.

A further object of this invention is to provide a pharmaceutical composition comprising said amidine derivatives or a pharmaceutically acceptable salt thereof.

Still further object of this invention is to provide a use of said amidine derivatives or a pharmaceutically acceptable salt thereof as a medicament for prophylactic and therapeutic treatment of NOS-mediated diseases such as adult respiratory distress syndrome, myocarditis, synovitis, septic shock, insulin-dependent diabetes mellitis, ulcerative colitis, cerebral infarction, rheumatoid arthritis, osteoarthritis, osteoporosis, systemic lupus erythematosis, organ transplantation, asthma, pain, ulcer, and the like in human being and animals.

DISCLOSURE OF INVENTION :

The object amidine derivatives of the present invention are novel and can be represented by the following general formula (I) :

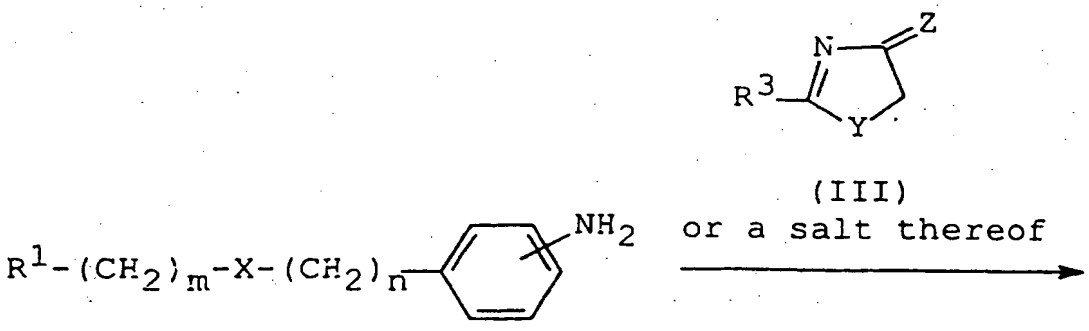


(I)

wherein R^1 is heterocyclic group,
X is $(CH_2)_a$ in which a is 0 or 1, O or S,
Y is CH_2, O, S or $N-R^2$
in which R^2 is hydrogen or lower alkyl,
Z is O or H_2, and
m and n are each 0 or 1.

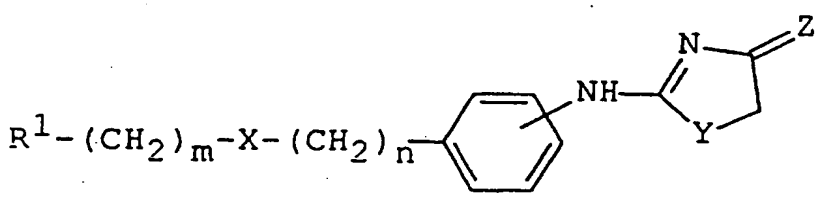
The object compound (I) of the present invention can be prepared by the following processes.

Process 1



(II)
or a salt thereof

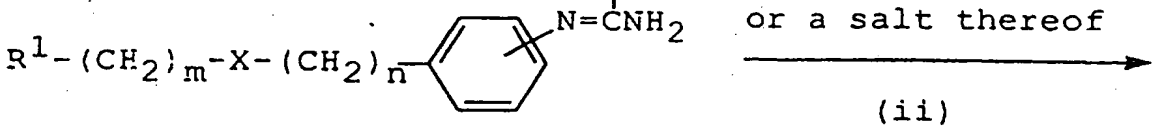
(III)
or a salt thereof



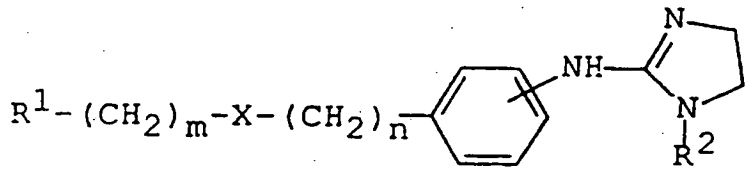
(I)
or a salt thereof

Process 2

(IV)
or a salt thereof

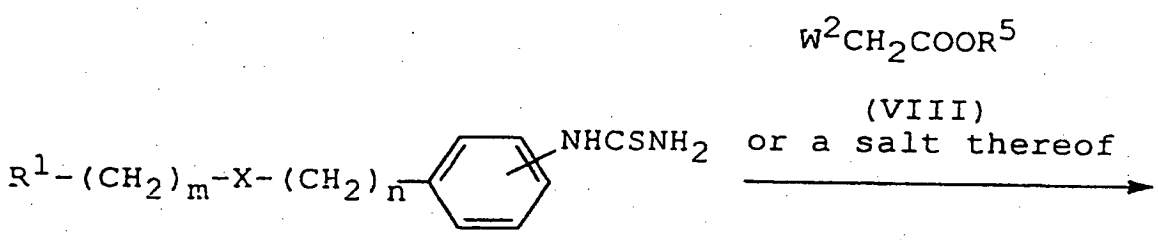


(VI)
or a salt thereof



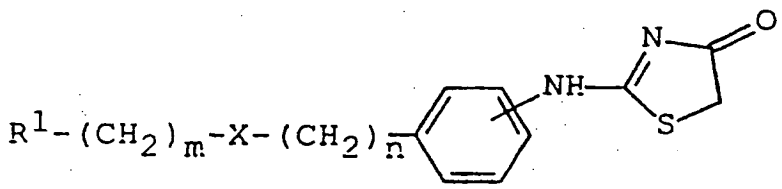
(I-a)
or a salt thereof

Process 3



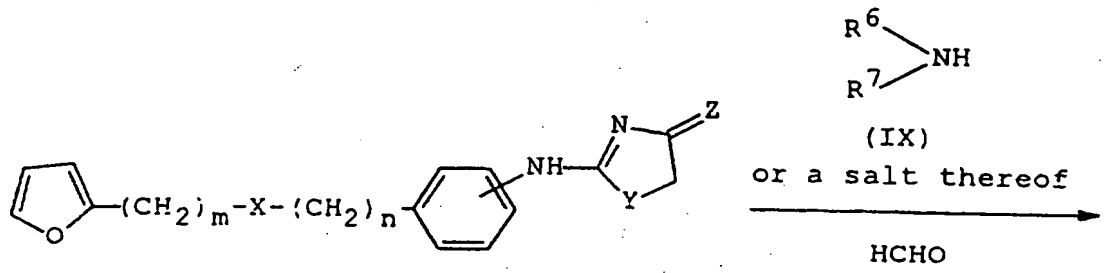
(IV)
or a salt thereof

(VIII)
or a salt thereof



(I-b)
or a salt thereof

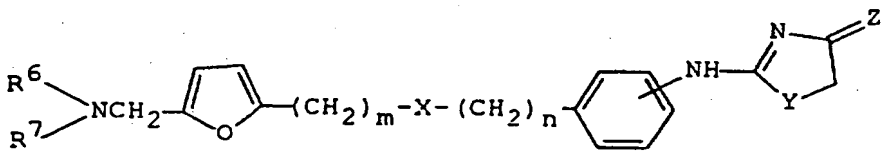
Process 4



(I-c)
or a salt thereof

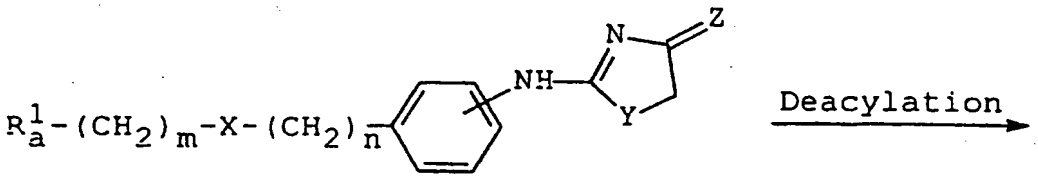
(IX)
or a salt thereof

HCHO

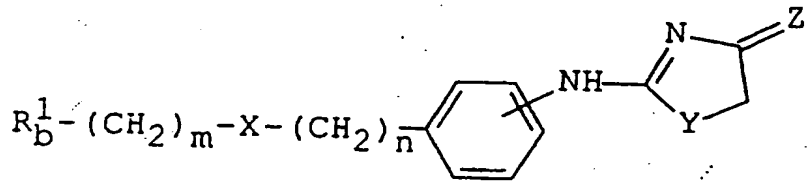


(I-d)
or a slat thereof

Process 5

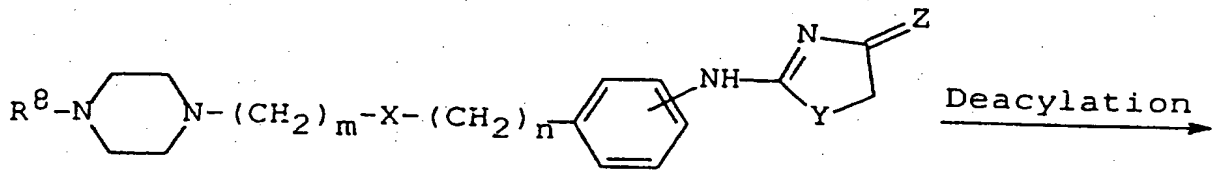


(I-e)
or a salt thereof

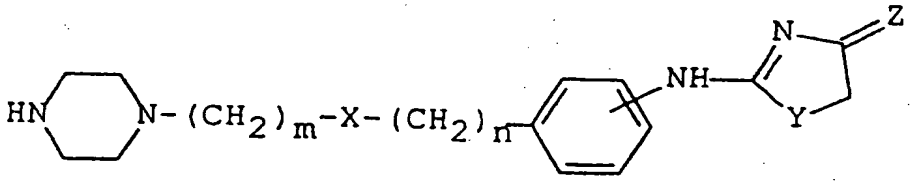


(I-f)
or a salt thereof

Process 6

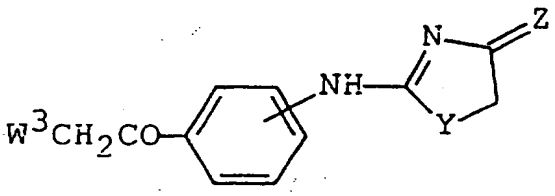


(I-g)
or a salt thereof



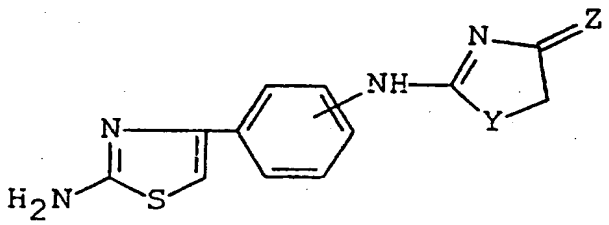
(I-h)
or a salt thereof

Process 7



(X)
or a salt thereof

Thiourea



(I-i)
or a salt thereof

wherein R^1, R^2, X, Y, Z, m and n are each as defined above,
R^3 is lower alkylthio or halogen,
R^4, R^5, R^6 and R^7 are each lower alkyl,
R^8 is acyl,
R^1_a is heterocyclic group having acylamino,
R^1_b is heterocyclic group having amino, and
W^1, W^2 and W^3 are each halogen.

The starting compounds can be prepared by the

Preparations as mentioned below or by conventional methods.

Suitable pharmaceutically acceptable salts of the objec compound (I) are conventional non-toxic salts and may includ a salt with a base or an acid addition salt such as a salt with an inorganic base, for example, an alkali metal salt (e.g., sodium salt, potassium salt, etc.), an alkaline earth metal salt (e.g., calcium salt, magnesium salt, etc.), an ammonium salt; a salt with an organic base, for example, an organic amine salt (e.g., triethylamine salt, pyridine salt, picoline salt, ethanolamine salt, triethanolamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, etc.); an inorganic acid addition salt (e.g., hydrochloride, hydrobromide, sulfate, phosphate, etc.); an organic carboxylic or sulfonic acid addition salt (e.g., formate, acetate, trifluoroacetate, maleate, tartrate, citrate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.); a salt with a basic or acidic amino acid (e.g., arginine, aspartic acid, glutamic acid, etc.).

In the above and subsequent descriptions of the present specification, suitable examples and illustration of the various definitions which the present invention intends to include within the scope thereof are explained in detail as follows.

The term "lower" is used to intend a group having 1 to 6, preferably 1 to 4, carbon atom(s), unless otherwise provided.

Suitable "lower alkyl" and "lower alkyl moiety" in the terms "lower alkylthio" may include straight or branched one having 1 to 6 carbon atom(s), such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, tert-pentyl, hexyl, and the like, and in which more preferable example may be C_1-C_4 alkyl.

Suitable "halogen" may be chloro, bromo, fluoro and iodo.

Suitable "heterocyclic group" may include saturated or unsaturated, monocyclic or polycyclic heterocyclic group containing at least one hetero-atom such as an oxygen, sulfur, nitrogen atom and the like.

And, especially preferable heterocyclic group may be heterocyclic group such as

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolyl, pyrrolinyl, imidazolyl, pyrazolyl, pyridyl, dihydropyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, triazolyl (e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl, etc.), tetrazolyl (e.g., 1H-tetrazolyl, 2H-tetrazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 4 nitrogen atom(s), for example, pyrrolidinyl, imidazolidinyl, piperidyl, piperazinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 4 nitrogen atom(s), for example, indolyl, isoindolyl, indolinyl, indolizinyl, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, imidazopyridyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl, etc.), etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, morpholinyl, sydnonyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 oxygen atom(s) and 1 to 3 nitrogen atom(s), for example, benzoxazolyl, benzoxadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiazolyl, isothiazolyl, thiadiazolyl (e.g., 1,2,3-thiadiazolyl, 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl, etc.), dihydrothiazinyl, etc.;

saturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, thiomorpholinyl, thiazolidinyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing 1 to 2 sulfur atom(s), for example, thienyl, dihydrodithiinyl, dihydrodithionyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s) and 1 to 3 nitrogen atom(s), for example, benzothiazolyl, benzothiadiazolyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom, for example, furyl, etc.;

unsaturated 3 to 8-membered (more preferably 5 or 6-membered) heteromonocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, dihydrooxathiinyl, etc.;

unsaturated condensed heterocyclic group containing 1 to 2 sulfur atom(s), for example, benzothienyl, benzodithiinyl, etc.;

unsaturated condensed heterocyclic group containing an oxygen atom and 1 to 2 sulfur atom(s), for example, benzoxathiinyl, etc.; and the like.

The heterocyclic moiety as stated above may have one to two, same or different, suitable substituent(s) such as lower alkyl as exemplified above, lower alkoxy (e.g. methoxy, etc.), acylamino such as lower alkanoylamino (e.g.

acetylamino, etc.), amino, dilower alkylaminomethyl wherein lower alkyl moiety is as exemplified above, halogen as exemplified above, acyl such as lower alkanoyl (e.g. acetyl, etc.) and diaminomethyleneamino.

Suitable "heterocyclic group having acylamino" may include heterocyclic group as mentioned above which is substituted by acylamino such as lower alkanoylamino (e.g. formylamino, acetylamino, propionylamino, butyrylamino, isobutyrylamino, valerylamino, isovalerylamino, pivaloylamino, hexanoylamino, etc.), for example, acetamidopyrimidinyl, and the like.

Suitable "heterocyclic group having amino" may include heterocyclic group as mentioned above which is substituted by amino, for example, aminopyrimidinyl, and the like.

Suitable "acyl" may include lower alkanoyl such as formyl, acetyl, propionyl, butyryl, isobutyryl, and the like.

Particularly, the preferred embodiment of R^1 is as follows.

R^1 is pyridyl having amino, pyridyl having lower alkanoylamino, pyrimidinyl having amino, pyrimidinyl having lower alkanoylamino, furyl, furyl having N,N-di(lower)alkylaminomethyl, thiazolyl having diaminomethyleneamino, thiazolyl having amino, thiazolyl having lower alkanoylamino, pyrrolidinyl, morpholinyl, piperazinyl, piperazinyl having lower alkanoyl, imidazolyl, imidazolyl having lower alkyl, and imidazopyridyl which may have one to two substituent(s) selected from the group consisting of lower alkyl, lower alkoxy and halogen.

Furthermore, the preferred embodiment of R^1 is as follows.

R^1 is 6-amino-2-pyridyl, 6-acetamido-2-pyridyl, 2-amino-4-pyrimidinyl, 2-acetamido-4-pyrimidinyl, 2-furyl, 5-dimethylaminomethyl-2-furyl, 2-diaminomethyleneamino-4-thiazolyl, 2-amino-4-thiazolyl, 2-acetamido-4-thiazolyl, 1-pyrrolidinyl, morpholino, 1-piperazinyl, 4-acetyl-1-piperazinyl, 2-imidazolyl, 2-methyl-1-imidazolyl, imidazo[1,2-a]-pyridin-2-yl, 7-methylimidazo[1,2-a]pyridin-2-yl, 7-methoxyimidazo[1,2-a]pyridin-2-yl, 3,7-dimethylimidazo[1,2-a]pyridin-2-yl, and 3-chloro-7-methylimidazo[1,2-a]pyridin-2-yl.

The processes for preparing the object compound (I) of the present invention are explained in detail in the following.

Process 1

The object compound (I) or a salt thereof can be prepared by reacting the compound (II) or a salt thereof with the compound (III) or a salt thereof.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as alcohol [e.g. methanol, ethanol, propanol, 2-methoxyethanol, etc.], tetrahydrofuran, dioxane, dimethyl sulfoxide, N,N-dimethylformamide or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming or heating.

Process 2-(i)

The compound (VI) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (V) or a salt thereof.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such

as alcohol [e.g. methanol, ethanol, propanol, etc.], tetrahydrofuran, dioxane, dimethyl sulfoxide, N,N-dimethylformamide or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming or heating.

Process 2-(ii)

The object compound (I-a) or a salt thereof can be prepared by reacting the compound (VI) or a salt thereof with the compound (VII) or a salt thereof.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as alcohol [e.g. methanol, ethanol, propanol, etc.], tetrahydrofuran, dioxane, dimethyl sulfoxide, N,N-dimethylformamide or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming or heating.

Process 3

The object compound (I-b) or a salt thereof can be prepared by reacting the compound (IV) or a salt thereof with the compound (VIII) or a salt thereof.

This reaction is usually carried out in a conventional solvent which does not adversely influence the reaction such as alcohol [e.g. methanol, ethanol, propanol, etc.], tetrahydrofuran, dioxane, dimethyl sulfoxide, N,N-dimethylformamide or a mixture thereof.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming or heating.

Process 4

The object compound (I-d) or a salt thereof can be

prepared by reacting the compound (I-c) or a salt thereof with the compound (IX) or a salt thereof.

The compound (IX) or a salt thereof is used with formalin.

The reaction is usually carried out in a conventional solvent such as water, alcohol [e.g. methanol, ethanol, etc.], acetone, dioxane, acetonitrile, chloroform, dichloromethane, ethylene chloride, tetrahydrofuran, ethyl acetate, N,N-dimethylformamide, N,N-dimethylacetamide, pyridine or any other organic solvent which does not adversely influence the reaction.

The reaction temperature is not critical, and the reaction is usually carried out under cooling to heating.

The reaction may be carried out in the presence of an inorganic or organic base such as an alkali metal bicarbonate, tri(lower)alkylamine (e.g. triethylamine, etc.) pyridine, N-(lower)alkylmorphorine, N,N-di(lower)alkylbenzylamine, or the like.

The reaction may also be carried out in the presence of acetyl chloride.

The compound (IX) can be prepared by mixing di(lower)alkylamine hydrochloride with formalin.

Process 5

The object compound (I-f) or a salt thereof can be prepared by subjecting the compound (I-e) or a salt thereof to deacylation.

Suitable method for this deacylation reaction may include conventional one such as hydrolysis, reduction, or the like. The hydrolysis is preferably carried out in the presence of a base or an acid.

Suitable base may include, for example, an inorganic base such as alkali metal hydroxide (e.g. sodium hydroxide, potassium hydroxide, etc.), alkaline earth metal hydroxide (e.g. magnesium hydroxide, calcium hydroxide, etc.), alkali

metal carbonate (e.g. sodium carbonate, potassium carbonate, etc.), alkaline earth metal carbonate (e.g. magnesium carbonate, calcium carbonate, etc.), alkali metal bicarbonate (e.g. sodium bicarbonate, potassium bicarbonate, etc.), alkali metal acetate (e.g. sodium acetate, potassium acetate, etc.), alkaline earth metal phosphate (e.g. magnesium phosphate, calcium phosphate, etc.), alkali metal hydrogen phosphate (e.g. disodium hydrogen phosphate, dipotassium hydrogen phosphate, etc.), or the like, and an organic base such as tri(lower)alkylamine (e.g. trimethylamine, triethylamine, etc.), picoline, N-methylpyrrolidine, N-methylmorpholine, 1,5-diazabicyclo[4,3,0]non-5-one, 1,4-diazabicyclo[2,2,2]octane, 1,5-diazabicyclo[5,4,0]-undecene-5 or the like. The hydrolysis using a base is often carried out in water or a hydrophilic organic solvent or a mixed solvent thereof.

Suitable acid may include an organic acid (e.g. formic acid, acetic acid, propionic acid, etc.) and an inorganic acid (e.g. hydrochloric acid, hydrobromic acid, sulfuric acid, etc.).

The present hydrolysis is usually carried out in an organic solvent, water or a mixed solvent thereof.

The reaction temperature is not critical, and the reaction is usually carried out at ambient temperature or under warming or heating.

Process 6

The object compound (I-h) or a salt thereof can be prepared by subjecting the compound (I-g) or a salt thereof to deacylation.

The reaction can be carried out in substantially the same manner as Process 5, and therefore the reaction mode and reaction conditions [e.g. solvent, reaction temperature, etc.] of this reaction are to be referred to those as explained in Process 5.

Process 7

The object compound (I-i) or a salt thereof can be prepared by reacting the compound (X) or a salt thereof with thiourea.

This reaction is usually conducted in a conventional solvent which does not adversely influence the reaction such as methyl acetate, dichloromethane, chloroform, carbon tetrachloride, tetrahydrofuran, acetone, N,N-dimethylformamide, N,N-dimethylacetamide, dioxane, water, alcohol [e.g. methanol, ethanol, etc.] acetic acid, formic acid, etc. or a mixture thereof.

The reaction temperature is not critical and the reaction is usually conducted under cooling to heating.

Suitable salts of the object and starting compounds in Processes (1), (2), (3), (4), (5), (6) and (7) can be referred to the ones as exemplified for the compound (I).

The compounds obtained by the above processes can be isolated and purified by a conventional method such as pulverization, recrystallization, column chromatography, reprecipitation, or the like.

It is to be noted that the compound (I) and the other compounds may include one or more stereoisomer(s) such as optical isomer(s) and geometrical isomer(s) due to asymmetric carbon atom(s) and double bond(s), and all or such isomers and mixture thereof are included within the scope of this invention.

The object compound (I) and a pharmaceutically acceptable salt thereof may include a solvate [e.g., enclosure compound (e.g., hydrate, etc.)].

The object compounds (I) and pharmaceutically acceptable salts thereof possess a strong inhibitory activity on the production of nitric oxide (NO).

Accordingly, the object compounds (I) and pharmaceutically acceptable salts thereof are expected to

possess a nitric oxide synthase (NOS)-inhibitory activity or a NOS-production inhibitory activity.

Accordingly, they are useful for prevention and/or treatment of adult respiratory distress syndrome, myocarditis, synovitis, septic shock, insulin-dependent diabetes mellitis; ulcerative colitis, cerebral infarction, rheumatoid arthritis, osteoarthritis, osteoporosis, systemic lupus erythematosis, organ transplantation, asthma, pain, ulcer, and the like.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the representative compound of the compound (I) are shown in the following.

Test Compound

(a) 2-[4-[2-(7-Methylimidazo[1,2-a]pyridin-2-yl)ethyl]-phenylamino]-2-thiazoline

Test

Binding assay using nitric oxide synthase (NOS)

Test Method

A crude preparation of NOS obtained from the brains of male SD rats. The whole brain (including cerebellum) was homogenized in 5 volume (W/V) of 50 mM Tris buffer (pH 7.0 at 4°C), centrifuged at 48,000 x g for 20 minutes, the pellet discarded and the supernatant passed through 1/4 volume (V/V) of Dowex AG50WX-8 resin (Na^+ form), in order to remove of endogenous arginine. The supernatant was collected, the pH adjusted to 7.0 at 22°C and this cytosolic preparation was frozen and stored at -80°C until required. In the binding assay, each drug was incubated with the brain cytozole (200

μg protein/tube) in a final volume of 0.15 ml of 50 mM Tris buffer including 10 μM $CaCl_2$ and 10 nM ^{3}[H]Na (Amersham, Amersham, UK). Incubations were performed at 27°C for 90 minutes and were terminated by vacuum filtration over 0.3 % polyethyleneimine pretreated GF/B glass fibre filters which were subsequently washed with 4 ml x 4 of 4°C distilled water. Non specific binding was defined by use of 100 μM Na. Data were expressed as inhibition % of specific binding.

Test Result

Test Compound (a)	Inhibition (%)
10^{-5} g/ml	95

For therapeutic administration, the object compounds (I) of the present invention and pharmaceutically acceptable salts thereof are used in a form of the conventional pharmaceutical preparation in admixture with a conventional pharmaceutically acceptable carrier such as an organic or inorganic solid or liquid excipient which is suitable for oral, parenteral or external administration.
The pharmaceutical preparation may be compounded in a solid form such as granule, capsule, tablet, dragee or suppository, or in a liquid form such as solution, suspension or emulsion for injection, ingestion, eye drops, etc. If needed, there may be included in the above preparation auxiliary substance such as stabilizing agent, wetting or emulsifying agent, buffer or any other commonly used additives.

The effective ingredient may usually be administered with a unit dose of 0.001 mg/kg to 500 mg/kg, preferably 0.01 mg/kg to 10 mg/kg, 1 to 4 times a day. However, the above dosage may be increased or decreased according to age, weight and conditions of the patient or the administering method.

The following Preparations and Examples are given for the purpose of illustrating the present invention in detail.

Preparation 1

A solution of 2-chloromethyl-7-methylimidazo[1,2-a]-pyridine (6.8 g) and sodium 4-nitrophenyl sulfide (6.7 g) in N,N-dimethylformamide (35 ml) was stirred for two hours at ambient temperature. The reaction mixture was poured into water (175 ml) and the resulting precipitate was collected by filtration. Recrystallization from ethanol afforded 7-methyl-2-(4-nitrophenyl)thiomethylimidazo[1,2-a]pyridine (5.5 g).

mp : 150-151°C

IR (Nujol) : 1575, 1330 cm^{-1}

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 4.48 (2H, s), 6.70 (1H, dd, J=2Hz and 7Hz), 7.27 (1H, d, J=2Hz), 7.60 (2H, d, J=9Hz), 7.82 (1H, s), 8.12 (2H, d, J=9Hz), 8.35 (1H, d, J=7Hz)

Preparation 2

2-(Diaminomethyleneamino)-4-(4-nitrophenyl)-thiomethylthiazole was prepared from 4-chloromethyl-2-(diaminomethyleneamino)thiazole hydrochloride in a similar manner to that of Preparation 1.

mp : 173-174°C

IR (Nujol) : 3410, 1710, 1665, 1545, 1335 cm^{-1}

NMR (DMSO-d_6, δ) : 4.30 (2H, s), 6.65 (1H, s), 6.82 (4H, s), 7.63 (2H, d, J=9Hz), 8.16 (2H, d, J=9Hz)

Preparation 3

A suspension of 2-chloromethyl-7-methylimidazo[1,2-a]-pyridine (4.0 g) and sodium 4-nitrophenyl oxide (4.0 g) in N,N-dimethylformamide (20 ml) was stirred at 60°C for 19 hours. The reaction mixture was poured into water (100 ml)

and the resulting precipitate was collected by filtration. Recrystallization from a mixture of methanol - dioxane afforded 7-methyl-2-(4-nitrophenoxy)methylimidazo[1,2-a]-pyridine (2.6 g).

mp : 199-200°C

IR (Nujol) : 1510, 1335 cm^{-1}

NMR (DMSO-d_6, δ) : 2.35 (3H, s), 5.35 (2H, s), 6.77 (1H, dd, J=2Hz and 7Hz), 7.28 (2H, d, J=9Hz), 7.32 (1H, d, J=2Hz), 7.93 (1H, s), 8.21 (2H, d, J=9Hz), 8.41 (1H, d, J=7Hz)

Preparation 4

7-Methyl-2-(4-nitrophenoxy)methylimidazo[1,2-a]pyridine (2.5 g) was added portionwise to a stirred mixture of iron powder (2.0 g) and ammonium chloride (0.24 g) in refluxing ethanol (25 ml) and water (2.5 ml). After being stirred for an hour, the mixture was filtered and the filtrate was concentrated in vacuo. The residue was added to saturated aqueous sodium bicarbonate and extracted with dichloromethane. The extract was dried over anhydrous magnesium sulfate and concentrated in vacuo to afford 2-(4-aminophenoxy)methyl-7-methylimidazo[1,2-a]pyridine (1.4 g).

mp : 149-150°C

IR (Nujol) : 3420, 3320, 3200, 3145 cm^{-1}

NMR (DMSO-d_6, δ) : 2.33 (3H, s), 4.58 (2H, s), 5.02 (2H, s), 6.51 (2H, d, J=9Hz), 6.70 (1H, dd, J=2Hz and 7Hz), 6.78 (2H, d, J=9Hz), 7.28 (1H, d, J=2Hz), 7.80 (1H, s), 8.36 (1H, d, J=7Hz)

Preparation 5

The following compounds were prepared according to a similar manner to that of Preparation 4.

(1) 2-(4-Aminophenyl)thiomethyl-7-methylimidazo[1,2-a]-pyridine

mp : 130-133°C

IR (Nujol) : 3450, 3290, 3160, 3135 cm^{-1}

NMR (DMSO-d_6, δ) : 2.32 (3H, s), 4.07 (2H, s), 5.00 (2H, br s), 6.55 (2H, d, J=8Hz), 6.68 (1H, dd, J=2Hz and 7Hz), 7.13 (2H, d, J=8Hz), 7.27 (1H, d, J=2Hz), 7.62 (1H, s), 8.33 (1H, d, J=7Hz)

(2) 4-(4-Aminophenyl)thiomethyl-2-(diaminomethyleneamino)-thiazole

mp : 175-176°C

IR (Nujol) : 3425, 3310, 3110, 1715, 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 3.80 (2H, s), 5.17 (2H, br s), 6.28 (1H, s), 6.50 (2H, d, J=8Hz), 6.80 (4H, s), 7.07 (2H, d, J=8Hz)

Preparation 6

Benzoyl chloride (1 ml) was added dropwise under reflux to stirred solution of ammonium thiocyanate (0.73 g) in acetone (20 ml). The mixture was stirred under reflux for 15 minutes, and then 2-[2-(4-aminophenyl)ethyl]-3,7-dimethylimidazo[1,2-a]pyridine (2.2 g) in acetone (10 ml) was added dropwise. After the resulting mixture was stirred under reflux for further four hours, concentrated in vacuo and mixed with ethyl acetate (20 ml) and water (50 ml). The resulting precipitate was collected by filtration and recrystallized from ethanol - n-hexane to afford 1-benzoyl-3-[4-[2-(3,7-dimethylimidazo[1,2-a]pyridin-2-yl)ethyl]phenyl]thiourea (3.0 g).

mp : 171-172°C

IR (Nujol) : 1665 cm^{-1}

NMR (DMSO-d_6, δ) : 2.31 (3H, s), 2.50 (3H, s), 3.07 (4H, s), 7.18 (1H, dd, J=2Hz and 7Hz), 7.25 (1H, d, J=8Hz), 7.51 (1H, d, J=2Hz), 7.59 (5H, s), 7.94 (1H, d, J=8Hz), 8.40 (1H, d, J=7Hz), 11.44 (1H, br s), 12.53 (1H, s)

Preparation 7

A mixture of 1-benzoyl-3-[4-[2-(3,7-dimethylimidazo-[1,2-a]pyridin-2-yl)ethyl]phenyl]thiourea (6.3 g) and sodium hydroxide (0.59 g) in methanol (60 ml) was stirred at 60°C for 20 minutes. After concentration, the residue was mixed with water (30 ml) and the resulting precipitate was collected by filtration and recrystallized from methanol - tetrahydrofuran to afford 4-[2-(3,7-dimethylimidazo[1,2-a]-pyridin-2-yl)ethyl]phenylthiourea (4.45 g).

mp : 194-195°C

IR (Nujol) : 3400, 3265, 3170 cm^{-1}

NMR (DMSO-d_6, δ) : 2.25 (3H, s), 2.33 (3H, s), 2.92 (4H, s), 6.68 (1H, dd, J=2Hz and 7Hz), 7.13 (2H, d, J=9Hz), 7.24 (2H, s), 7.29 (2H, d, J=9Hz), 7.31 (1H, d, J=2Hz), 7.98 (1H, d, J=7Hz), 9.56 (1H, s)

Preparation 8

A solution of 4'-nitrophenyl-4-pentanone (6.7 g) and bromine (5.43 g) in methanol (70 ml) was stirred at room temperature for 5 hours. N-acetylthiourea (3.82 g) and potassium carbonate (11.17 g) were added to the reaction mixture. The mixture was heated at 50°C for 4 hours. The solvent was removed under reduced pressure and the residue was dissolved in a mixture of water (100 ml) and tetrahydrofuran (30 ml). The mixture was extracted with ethyl acetate (120 ml) and the extract was dried over magnesium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with chloroform:methanol = 100:1. The appropriate fractions was collected to afford 2-acetylamino-4-[3-(4-nitrophenyl)propyl]thiazole (1.0 g).

mp : 147-148°C

IR (Nujol) : 3150, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 1.89-2.04 (2H, m), 2.11 (3H, s),

2.61 (2H, t, J=7.4Hz), 2.75 (2H, t, J=7.4Hz), 6.77 (1H, s), 7.49 (2H, d, J=8.7Hz), 8.16 (2H, d, J=8.7Hz), 12.04 (1H, s)

Preparation 9

Triphenylphosphine (1.21 g) was added to a solution of p-nitrobenzyl bromide (1.0 g) in N,N-dimethylformamide (10 ml) at room temperature. The mixture was stirred at room temperature for 3.5 hours. 2-Acetylamino-4-formylthiazole (1.18 g) and potassium t-butoxide (620 mg) were added to the reaction mixture and then the mixture was stirred at room temperature for 21 hours. The solvent was removed under reduced pressure. The residue was suspended in toluene (20 ml). The mixture was stirred for 30 minutes at room temperature and then the insoluble material was removed by filtration. The solvent was removed under reduced pressure and the residue was chromatographed on a silica gel column eluting with a mixture of ethyl acetate:methanol = 50:1 and then chloroform:methanol = 100:1. The appropriate fractions was collected and the solvent was removed under reduced pressure. Crystallization from diisopropyl ether afford 2-acetylamino-4-((E)-4-nitrophenylvinyl)thiazole (700 mg).

mp : 197-198°C

IR (Nujol) : 3330, 1680, 1670, 1620, 1540 cm^{-1}

NMR (DMSO-d_6, δ) : 2.14 (3H, s), 6.60-6.74 (2H, m), 7.16 (1H, s), 7.79 (2H, d, J=8.6Hz), 8.17 (2H, d, J=8.6Hz), 11.94 (1H, br s)

Preparation 10

A mixture of 2-acetylamino-4-((E)-4-nitrophenylvinyl)-thiazole (4.5 g) and palladium on activated carbon (wet) (1.9 g) in methanol (45 ml) and tetrahydrofuran (65 ml) was stirred at room temperature for 8.5 hours under hydrogen stream. The insoluble material was removed by filtration. The solvent was removed under reduced pressure and the

residue was chromatographed on a silica gel column eluting with chloroform:methanol = 50:1. Crystallization from ethyl acetate afford 2-acetylamino-4-[2-(4-aminophenyl)ethyl]-thiazole (2.3 g).

mp : 135-136°C

IR (Nujol) : 3370, 1650 cm^{-1}

NMR (DMSO-d_6, δ) : 2.11 (3H, s), 2.76 (4H, br s), 4.83 (2H, s), 6.46 (2H, d, J=8.3Hz), 6.84 (2H, d, J=8.3Hz), 12.08 (1H, br s)

Example 1

A solution of 2-[2-(3-aminophenyl)ethyl]-3,7-dimethylimidazo[1,2-a]pyridine (1.0 g) and 2-methylthio-2-thiazoline hydriodide (1.1 g) in dimethylsulfoxide (10 ml) was stirred at 100°C for 20 hours. After concentration, the residue was added to saturated aqueous sodium bicarbonate and extracted with dichloromethane. The extract was dried over magnesium sulfate and concentrated in vacuo to give a residue, which was chromatographed on silica gel eluting with chloroform - methanol (100/1). The free base obtained was converted to the difumarate in the usual manner, and the salt was recrystallized from methanol to afford 2-[3-[2-(3,7-dimethylimidazo[1,2-a]pyridin-2-yl)ethyl]phenylamino]-2-thiazoline difumarate (0.64 g).

mp : 157°C (decomp.)

IR (Nujol) : 1690, 1670, 1645 cm^{-1}

NMR (DMSO-d_6, δ) : 2.22 (3H, s), 2.42 (3H, s), 2.97 (4H, s), 3.23 (2H, t, J=7Hz), 3.87 (2H, t, J=7Hz), 6.67 (4H, s), 6.82-6.93 (1H, m), 6.95 (1H, dd, J=2Hz and 7Hz), 7.13-7.22 (3H, m), 7.50 (1H, d, J=2Hz), 8.19 (1H, d, J=7Hz), 10.57 (5H, s)

Example 2

The following compounds were prepared according to a similar manner to that of Example 1.

(1) 2-[4-[2-(Imidazo[1,2-a]pyridin-2-yl)ethyl]phenylamino]-2-thiazoline

mp : 160-161°C

IR (Nujol) : 3280, 3220, 3150, 1625 cm^{-1}

NMR (DMSO-d_6, δ) : 2.95 (4H, s), 3.27 (2H, t, J=7Hz), 3.92 (2H, t, J=7Hz), 6.80 (1H, dt, J=2Hz and 7Hz), 7.10 (2H, d, J=8.5Hz), 7.13-7.50 (2H, m), 7.38 (2H, d, J=8.5Hz), 7.63 (1H, s), 8.42 (1H, dd, J=2Hz and 7Hz)

(2) 2-[4-[2-(7-Methylimidazo[1,2-a]pyridin-2-yl)ethyl]phenylamino]-2-thiazoline

mp : 185-186°C

IR (Nujol) : 3240, 3175, 3100, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.33 (3H, s), 2.93 (4H, s), 3.28 (2H, t, J=7Hz), 3.93 (2H, t, J=7Hz), 6.67 (1H, dd, J=2Hz and 7Hz), 7.12 (2H, d, J=8Hz), 7.27 (1H, d, J=2Hz), 7.40 (2H, d, J=8Hz), 7.55 (1H, s), 8.33 (1H, d, J=7Hz)

(3) 2-[4-[2-(7-Methoxyimidazo[1,2-a]pyridin-2-yl)ethyl]phenylamino]-2-thiazoline

mp : 180-181°C

IR (Nujol) : 3220, 3165, 3090, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.92 (4H, s), 3.28 (2H, t, J=7Hz), 3.82 (3H, s), 3.93 (2H, t, J=7Hz), 6.55 (1H, dd, J=2Hz and 7Hz), 6.88 (1H, d, J=2Hz), 7.13 (2H, d, J=9Hz), 7.41 (2H, d, J=9Hz), 7.47 (1H, s), 8.28 (1H, d, J=7Hz)

(4) 2-[4-[2-(3,7-Dimethylimidazo[1,2-a]pyridin-2-yl)ethyl]phenylamino]-2-thiazoline

mp : 202-203°C

IR (Nujol) : 3240, 3180, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.20 (3H, s), 2.33 (3H, s),

2.87 (4H, s), 3.27 (2H, t, J=7Hz), 3.91 (2H, t, J=7Hz), 6.70 (1H, dd, J=1.5Hz and 7Hz), 7.06 (2H, d, J=9Hz), 7.26 (1H, d, J=1.5Hz), 7.36 (2H, d, J=9Hz), 8.03 (1H, d, J=7Hz), 8.78 (1H, br s)

(5) 2-[4-[(7-Methylimidazo[1,2-a]pyridin-2-yl)methoxy]phenylamino]-2-thiazoline
mp : 196-197°C
IR (Nujol) : 1615 cm^{-1}
NMR (DMSO-d_6, δ) : 2.33 (3H, s), 3.27 (2H, t, J=7Hz), 3.90 (2H, t, J=7Hz), 5.12 (2H, s), 6.72 (1H, dd, J=1.5Hz and 7Hz), 6.94 (2H, d, J=9Hz), 7.30 (1H, d, J=1.5Hz), 7.38 (2H, d, J=9Hz), 7.85 (1H, s), 8.38 (1H, d, J=7Hz), 8.65 (1H, br s)

(6) 2-[4-[(7-Methylimidazo[1,2-a]pyridin-2-yl)methylthio]phenylamino]-2-thiazoline
mp : 162-163°C
IR (Nujol) : 1625 cm^{-1}
NMR (DMSO-d_6, δ) : 2.32 (3H, s), 3.28 (2H, t, J=7Hz), 3.93 (2H, t, J=7Hz), 4.20 (2H, s), 6.67 (1H, dd, J=1.5Hz and 7Hz), 7.25 (1H, d, J=1.5Hz), 7.26 (2H, d, J=9Hz), 7.44 (2H, d, J=9Hz), 7.65 (1H, s), 8.29 (1H, d, J=7Hz)

(7) 2-[4-[2-(3,7-Dimethylimidazo[1,2-a]pyridin-2-yl)ethyl]phenylamino]-2-oxazoline
mp : 206-207°C
IR (Nujol) : 3240, 1675 cm^{-1}
NMR (DMSO-d_6, δ) : 2.23 (3H, s), 2.33 (3H, s), 2.88 (4H, s), 3.36-3.45 (2H, m), 3.71-3.88 (2H, m), 6.66 (1H, dd, J=1.5Hz and 7Hz), 6.79 (1H, s), 7.07 (2H, d, J=9Hz), 7.18 (1H, d, J=1.5Hz), 7.39 (2H, d, J=9Hz), 7.97 (1H, d, J=7Hz)

(8) 2-[4-[2-(3,7-Dimethylimidazo[1,2-a]pyridin-2-yl)ethyl]-phenylamino]-2-imidazolin-4-one

mp : >250°C

IR (Nujol) : 1680, 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 2.24 (3H, s), 2.53 (3H, s), 2.91-3.30 (4H, m), 4.32 (2H, s), 7.19 (1H, dd, J=2Hz and 7Hz), 7.27 (4H, s), 7.49 (1H, d, J=2Hz), 8.13 (1H, d, J=7Hz)

(9) 2-[4-[2-(Furan-2-yl)ethyl]phenylamino]-2-thiazoline

IR (Film) : 1635 cm^{-1}

NMR (DMSO-d_6, δ) : 2.90 (4H, s), 3.27 (2H, t, J=7Hz), 3.92 (2H, t, J=7Hz), 6.07 (1H, dd, J=1Hz and 3Hz), 6.33 (1H, dd, J=2Hz and 3Hz), 7.08 (2H, d, J=9Hz), 7.38 (2H, d, J=9Hz), 7.50 (1H, dd, J=1Hz and 2Hz), 8.78 (1H, br s)

(10) 2-[[4-[2-(Diaminomethyleneamino)thiazol-4-yl]methylthio]phenylamino]-2-thiazoline fumarate

mp : 201-202°C

IR (Nujol) : 1670, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 3.30 (2H, t, J=7Hz), 3.95 (2H, t, J=7Hz), 4.05 (2H, s), 6.62 (2H, s), 7.18-7.62 (9H, m)

(11) 2-[4-[2-(6-Acetamidopyridin-2-yl)ethyl]phenylamino]-2-thiazoline

mp : 168-169°C

IR (Nujol) : 3170, 1700, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 2.12 (3H, s), 2.85-3.15 (4H, m), 3.28 (2H, t, J=7Hz), 3.93 (2H, t, J=7Hz), 6.95 (1H, dd, J=1Hz and 8Hz), 7.08 (2H, d, J=9Hz), 7.39 (2H, d, J=9Hz), 7.67 (1H, t, J=8Hz), 7.95 (1H, dd, J=1Hz and 8Hz), 8.78 (1H, br s), 10.40 (1H, s)

(12) 2-[4-[2-(2-Acetamidopyrimidin-4-yl)ethyl]phenylamino]-2-thiazoline

mp : 180-181°C

IR (Nujol) : 1680, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.22 (3H, s), 2.93 (4H, s), 3.25 (2H, t, J=7Hz), 3.89 (2H, t, J=7Hz), 6.95 (1H, d, J=5Hz), 7.03 (2H, d, J=8Hz), 7.30 (2H, d, J=8Hz), 8.41 (1H, d, J=5Hz), 8.70 (1H, br s), 10.26 (1H, br s)

Example 3

A suspension of 2-[4-[2-(7-methylimidazo[1,2-a]pyridin-2-yl)ethyl]phenylamino]-2-thiazoline (0.70 g) and N-chlorosuccinimide (0.29 g) in dichloromethane (10 ml) was stirred at ambient temperature for two hours. After washing with water, the reacting solution was dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from methanol to afford 2-[4-[2-(3-chloro-7-methylimidazo[1,2-a]pyridin-2-yl)ethyl]phenylamino]-2-thiazoline (0.35 g).

mp : 185-186°C

IR (Nujol) : 3260, 3195, 3125, 1635 cm^{-1}

NMR (DMSO-d_6, δ) : 2.37 (3H, s), 2.93 (4H, s), 3.26 (2H, t, J=7Hz), 3.90 (2H, t, J=7Hz), 6.83 (1H, dd, J=1.5Hz and 7Hz), 7.00 (2H, d, J=8Hz), 7.27 (2H, d, J=8Hz), 7.30 (1H, d, J=1.5Hz), 8.60 (1H, d, J=7Hz), 8.70 (1H, br s)

Example 4

Phosphorus oxychloride (0.34 ml) was added to a solution of 2-pyrrolidone (0.64 g) in dichloromethane (5 ml) with stirring at ambient temperature. After stirring for three hours, 2-[2-(4-aminophenyl)ethyl]-3,7-dimethylimidazo[1,2-a]-pyridine (1.0 g) and triethylamine (0.53 ml) were added to the solution and the mixture was stirred at ambient

temperature for further two hours. The reaction mixture was poured into water (20 ml). The aqueous layer separated was basified with saturated aqueous sodium bicarbonate and extracted with dichloromethane. The extract was dried over magnesium sulfate and concentrated in vacuo. The residue was recrystallized from a mixture of dichloromethane and diisopropyl ether to afford 2-[4-[2-(3,7-dimethylimidazo-[1,2-a]pyridin-2-yl)ethyl]phenylamino]-1-pyrroline (0.46 g).

mp : 195-196°C

IR (Nujol) : 3300, 1645 cm^{-1}

NMR (DMSO-d_6, δ) : 1.62-1.96 (2H, m), 2.20 (3H, s), 2.32 (3H, s), 2.37-2.56 (2H, m), 2.84 (4H, s), 3.55 (2H, t, J=6Hz), 6.66 (1H, dd, J=1Hz and 7Hz), 6.96 (2H, d, J=8Hz), 7.19 (1H, d, J=1Hz), 7.39 (2H, d, J=8Hz), 7.97 (1H, d, J=7Hz)

Example 5

A solution of 4-[2-(3,7-dimethylimidazo[1,2-a]pyridin-2-yl)ethyl]phenylthiourea (1.6 g) and methyl iodide (0.31 ml) in methanol (25 ml) was refluxed for two hours. After concentration, ethylenediamine (1 ml) and ethanol (25 ml) were added to the residue and the mixture was refluxed for two hours. The solvent was evaporated in vacuo. The residue was mixed with aqueous potassium carbonate and extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated in vacuo to give a residue, which was chromatographed on alumina eluting with chloroform - methanol (20/1) followed by recrystallization for dichloromethane - diisopropyl ether to afford 2-[4-[2-(3,7-dimethylimidazo-[1,2-a]pyridin-2-yl)ethyl]phenylamino]-2-imidazoline (0.46 g).

mp : 186-187°C

IR (Nujol) : 3425, 1660 cm^{-1}

NMR (DMSO-d_6, δ) : 2.27 (3H, s), 2.35 (3H, s), 2.87 (4H, s), 3.33 (4H, s), 5.88 (2H, br s), 6.73

(1H, dd, J=2Hz and 7Hz), 6.91 (2H, d, J=9Hz), 7.06 (2H, d, J=9Hz), 7.25 (1H, d, J=2Hz), 8.04 (1H, d, J=7Hz)

Example 6

The following compound was obtained according to a similar manner to that of Example 5.

2-[4-[2-(3,7-Dimethylimidazo[1,2-a]pyridin-2-yl)ethyl]-phenylamino]-1-methyl-2-imidazoline dihydrochloride

mp : 187-188°C

IR (Nujol) : 1640 cm^{-1}

NMR (DMSO-d_6, δ) : 2.42 (3H, s), 2.55 (3H, s), 3.13 (3H, s), 3.17 (4H, s), 3.65 (4H, s), 7.32 (4H, s), 7.36 (1H, d, J=7Hz), 7.73 (1H, s), 8.20 (1H, s), 8.61 (1H, d, J=7Hz), 10.83 (1H, s)

Example 7

A solution of 4-[2-(3,7-dimethylimidazo[1,2-a]pyridin-2-yl)ethyl]phenylthiourea (0.62 g) and ethyl chloroacetate (0.25 g) in N,N-dimethylformamide (10 ml) was stirred at 60°C for 22 hours. After concentration, the residue was mixed with aqueous sodium bicarbonate and extracted with dichloromethane. The extract was dried over magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel eluting with chloroform - methanol (20/1) and recrystallized from methanol - tetrahydrofuran to afford 2-[4-[2-(3,7-dimethylimidazo-[1,2-a]pyridin-2-yl)ethyl]phenylamino]-2-thiazolin-4-one (0.27 g).

mp : 257-258°C

IR (Nujol) : 1705, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.15 (3H, s), 2.35 (3H, s), 2.92 (4H, s), 3.90 (2H, s), 6.71 (1H, dd, J=2Hz and 7Hz), 7.05-7.67 (6H, m), 7.93 (1H, d, J=7Hz)

Example 8

Acetyl chloride (0.39 ml) was added dropwise to a solution of 2-[4-[2-(furan-2-yl)ethyl]phenylamino]-2-thiazoline (1.34 g) and pyridine (2.0 ml) in dichloromethane (25 ml) at 0°C. After being stirred for four hours, the mixture was poured into saturated aqueous sodium bicarbonate. The organic layer separated was dried over magnesium sulfate and concentrated in vacuo. The residue, 36% formalin (0.49 ml) and dimethylamine hydrochloride (0.53 g) were dissolved in acetic acid. After being stirred at 80°C for 1.5 hours, the solution was concentrated in vacuo. The residue was added to saturated aqueous sodium bicarbonate and extracted with dichloromethane. The extract was dried over magnesium sulfate and concentrated in vacuo to give a residue, which was chromatographed on silica gel eluting with chloroform - methanol (20/1). The free base obtained was converted to the fumarate in the usual manner, and the salt was recrystallized from ethanol - ether to afford 2-[4-[2-(5-dimethylaminomethylfuran-2-yl)ethyl]phenylamino]-2-thiazoline 3/2 fumarate.

mp : 144-145°C

IR (Nujol) : 1665 cm^{-1}

NMR (DMSO-d_6, δ) : 2.43 (6H, s), 2.87 (4H, s), 3.30 (2H, t, J=7Hz), 3.87 (2H, s), 3.93 (2H, t, J=7Hz), 6.04 (1H, d, J=3Hz), 6.38 (1H, d, J=3Hz), 6.61 (3H), 7.10 (2H, d, J=8Hz), 7.38 (2H, d, J=8Hz), 10.87 (4H, s)

Example 9

A solution of 2-[4-[2-(6-acetamidopyridin-2-yl)ethyl]phenylamino]-2-thiazoline (0.90 g) and concentrated hydrochloride (1.17 ml) in ethanol (18 ml) was refluxed for 7 hours with stirring. After concentration, the residue was added to 20% aqueous potassium carbonate and extracted with ethyl acetate. The extract was dried over magnesium sulfate

and concentrated in vacuo. The free base obtained was converted to the dihydrochloride in the usual manner, and the salt was recrystallized from ethanol - diisopropyl ether to afford 2-[4-[2-(6-aminopyridin-2-yl)ethyl]phenylamino]-2-thiazoline (0.71 g).

mp : 215-216°C

IR (Nujol) : 1655, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 3.08 (4H, s), 3.63 (2H, t, J=6Hz), 4.00 (2H, t, J=6Hz), 6.68-7.02 (2H, m), 7.23-7.55 (4H, m), 7.72-8.18 (4H, m)

Example 10

The following compound was prepared according to a similar manner to that of Example 9.

2-[4-[2-(2-Aminopyrimidin-4-yl)ethyl]phenylamino]-2-thiazoline

mp : 218-219°C

IR (Nujol) : 3310, 3120, 1630 cm^{-1}

NMR (DMSO-d_6, δ) : 2.79 (4H, s), 3.25 (2H, t, J=7Hz), 3.89 (2H, t, J=7Hz), 6.39 (1H, d, J=5Hz), 6.42 (2H, s), 7.02 (2H, d, J=9Hz), 7.27 (2H, d, J=9Hz), 8.03 (1H, d, J=5Hz), 8.45 (1H, br s)

Example 11

A solution of 1-(3-aminophenyl)methylpyrrolidine (0.35 g), 2-methylthio-2-thiazoline (0.27 g) and conc. hydrochloric acid (0.18 ml) in 2-methoxyethanol (5 ml) was stirred at 100°C for 8 hours. After concentration in vacuo, the residue was mixed with 20% aqueous potassium carbonate and extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated in vacuo. The free base obtained was converted to dioxalate in a usual manner and the salt was recrystallized from methanol-acetone-diisopropyl ether to afford 2-[3-(pyrrolidin-1-ylmethyl)phenylamino]-2-thiazoline

dioxalate (0.48 g).

mp : 195-196°C

IR (Nujol) : 1665, 1610 cm^{-1}

NMR (DMSO-d_6, δ) : 1.92 (4H, s), 3.19 (4H, s), 3.31 (2H, t, J=7Hz), 3.89 (2H, t, J=7Hz), 4.26 (2H, s), 7.11 (1H, d, J=7Hz), 7.27-7.34 (2H, m), 7.57 (1H, s)

Example 12

The following compounds were prepared according to a similar manner to that of Example 11.

(1) 2-[4-(Pyrrolidin-1-ylmethyl)phenylamino]-2-thiazoline dioxalate

NMR (DMSO-d_6, δ) : 1.92 (4H, s), 3.17 (4H, s), 3.30 (2H, t, J=7.5Hz), 3.94 (2H, t, J=7.5Hz), 4.22 (2H, s), 7.37 (2H, d, J=8.5Hz), 7.48 (2H, d, J=8.5Hz)

(2) 2-[3-(Imidazol-2-ylthiomethyl)phenylamino]-2-thiazoline dihydrochloride

NMR (DMSO-d_6, δ) : 3.60 (2H, t, J=7Hz), 3.97 (2H, t, J=7Hz), 4.71 (2H, s), 7.24-7.45 (4H, m), 7.67 (2H, s)

(3) 2-[3-(2-Methylimidazol-1-ylmethyl)phenylamino]-2-thiazoline

mp : 190-191°C

IR (Nujol) : 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 2.29 (3H, s), 3.26 (2H, t, J=7Hz), 3.88 (2H, t, J=7Hz), 5.13 (2H, s), 6.70 (1H, d, J=7.5Hz), 6.92 (1H, s), 7.17-7.25 (3H, m), 7.34 (1H, br s)

(4) 2-[4-[2-(2-Acetylaminothiazol-4-yl)ethyl]phenylamino]-2-thiazoline

mp : 215-216°C

IR (Nujol) : 3150, 1675, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 2.11 (3H, s), 2.84 (4H, s), 3.26 (2H, t, J=7.4Hz), 3.91 (2H, br s), 6.71 (1H, s), 7.03-7.07 (2H, m), 7.20-7.60 (3H, m), 12.00-12.50 (1H, m)

Anal. Calcd. for $C_{16}H_{18}N_4OS_2$: C 55.47, H 5.24, N 16.17
Found : C 55.20, H 5.22, N 15.90

(5) 2-[4-[2-(Morpholin-4-yl)ethyl]phenylamino]-2-thiazoline

mp : 137-138°C

IR (Nujol) : 3370, 1630, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 2.37-2.46 (6H, m), 2.61-2.68 (2H, m), 3.26 (2H, t, J=7.4Hz), 3.56 (4H, t, J=4.6Hz), 3.90 (2H, br s), 7.07 (2H, d, J=8.4Hz), 7.34 (2H, br s), 9.05 (1H, br)

(6) 2-[4-[2-(4-Acetylpiperazin-1-yl)ethyl]phenylamino]-2-thiazoline

mp : 162-163°C

IR (Nujol) : 3400, 1640, 1620, 1590 cm^{-1}

NMR (DMSO-d_6, δ) : 1.98 (3H, s), 2.36-2.44 (6H, m), 2.60-2.75 (2H, m), 3.26 (2H, t, J=7.5Hz), 3.35-3.45 (4H, m), 3.96 (2H, br), 7.07 (2H, d, J=8.4Hz), 7.45 (2H, br), 9.15 (1H, br)

Example 13

A solution of bromine (0.69 g) in acetonitrile (2 ml) was added dropwise to a solution of 2-(3-acetylphenylamino)-2-thiazoline hydrochloride (1.1 g) in methanol (10 ml) - dioxane (10 ml) at ambient temperature. After being stirred for one hour, the mixture was added to a suspension of thiourea (0.33 g) in ethanol (10 ml) and the whole mixture was refluxed for 6 hours. The resulting precipitate was collected by filtration and dissolved with water. The

solution was basified with 20% potassium carbonate and extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated in vacuo to give a residue. The free base was converted to dihydrochloride in a usual manner and the salt obtained was recrystallized from acetone-ethyl acetate to afford 2-[3-(2-aminothiazol-4-yl)phenylamino]-2-thiazoline dihydrochloride (0.50 g).

mp : >250°C

IR (Nujol) : 3300, 1625 cm^{-1}

NMR (DMSO-d_6, δ) : 3.61 (2H, t, J=7.5Hz), 3.99 (2H, t, J=7.5Hz), 7.29 (1H, s), 7.34 (1H, d, J=8.5Hz), 7.57 (1H, t, J=8.5Hz), 7.81 (1H, d, J=8.5Hz), 7.82 (1H, s)

Example 14

2-[4-[3-(2-Acetylaminothiazol-4-yl)propyl]phenylamino]-2-thiazoline was obtained from 2-acetylamino-4-[3-(4-nitrophenyl)propyl]thiazole according to a similar manner to that of Preparation 10 and then Example 11.

mp : 190-191°C

IR (Nujol) : 3120, 1620, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 1.80-1.93 (2H, m), 2.10 (3H, s), 2.50-2.61 (4H, m), 3.26 (2H, t, J=7.3Hz), 3.90 (2H, br s), 6.74 (1H, s), 7.05 (2H, d, J=8.3Hz), 7.45 (2H, br s), 12.01 (1H, br s)

Anal. Calcd. for $C_{17}H_{20}N_4OS_2$: C 56.64, H 5.59, N 15.54

Found : C 56.54, H 5.79, N 15.24

Example 15

A mixture of 2-[4-[2-(2-acetylaminothiazol-4-yl)ethyl]phenylamino]-2-thiazoline (1.0 g) and 6N hydrochloric acid (30 ml) was refluxed for 18 hours. The mixture was adjusted to pH 13.0 with potassium hydroxide and then was extracted with a mixture of ethyl acetate (70 ml) and tetrahydrofuran (70 ml). The extract was dried over

magnesium sulfate. The solvent was removed under reduced pressure. Recrystallization from a mixture of ethyl acetate and diisopropyl ether afford 2-[4-[2-(2-aminothiazol-4-yl)ethyl]phenylamino]-2-thiazoline (400 mg).

mp : 158-159°C

IR (Nujol) : 3420, 1620 cm^{-1}

NMR (DMSO-d_6, δ) : 2.55-2.70 (2H, m), 2.70-2.85 (2H, m), 3.26 (2H, t, J=7.4Hz), 3.92 (2H, br s), 6.09 (1H, s), 6.81 (2H, s), 7.05 (2H, d, J=8.3Hz), 7.35 (2H, br s)

Example 16

2-[4-(2-Piperazin-1-ylethyl)phenylamino]-2-thiazoline was obtained according to a similar manner to that of Example 15.

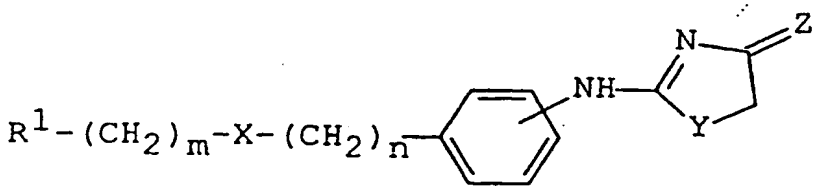
mp : 105-106°C

IR (Nujol) : 3240, 1630, 1600 cm^{-1}

NMR (DMSO-d_6, δ) : 2.32-2.44 (6H, m), 2.59-2.69 (6H, m), 3.26 (2H, t, J=7.2Hz), 3.80-4.00 (2H, m), 7.06 (2H, d, J=8.3Hz), 7.20-7.50 (2H, m)

C L A I M S

1. A compound of the formula :

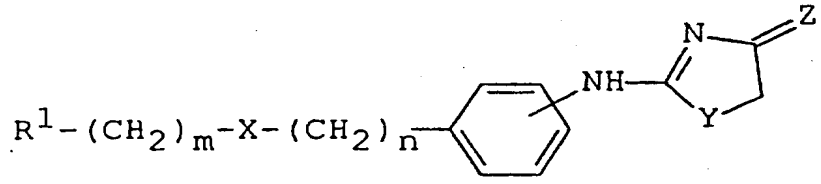


wherein R^1 is heterocyclic group,
X is $(CH_2)_a$ in which a is 0 or 1, O or S,
Y is CH_2, O, S or N-R^2
in which R^2 is hydrogen or lower alkyl,
Z is O or H_2, and
m and n are each 0 or 1,
and pharmaceutically acceptable salts thereof.

2. A compound of claim 1, wherein
R^1 is pyridyl having amino, pyridyl having lower alkanoylamino, pyrimidinyl having amino, pyrimidinyl having lower alkanoylamino, furyl, furyl having N,N-di(lower)alkylaminomethyl, thiazolyl having diaminomethyleneamino, thiazolyl having amino, thiazolyl having lower alkanoylamino, pyrrolidinyl, morpholinyl, piperazinyl, piperazinyl having lower alkanoyl, imidazolyl, imidazolyl having lower alkyl, and imidazopyridyl which may have one to two substituent(s) selected from the group consisting of lower alkyl, lower alkoxy and halogen.

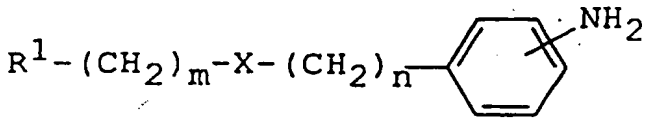
3. A compound of claim 2, wherein
R^1 is 6-amino-2-pyridyl, 6-acetamido-2-pyridyl, 2-amino-4-pyrimidinyl, 2-acetamido-4-pyrimidinyl, 2-furyl, 5-dimethylaminomethyl-2-furyl, 2-diaminomethyleneamino-4-thiazolyl, 2-amino-4-thiazolyl, 2-acetamido-4-thiazolyl, 1-pyrrolidinyl, morpholino, 1-piperazinyl, 4-acetyl-1-piperazinyl, 2-imidazolyl, 2-methyl-1-imidazolyl, imidazo-[1,2-a]pyridin-2-yl, 7-methylimidazo[1,2-a]pyridin-2-yl, 7-methoxyimidazo[1,2-a]pyridin-2-yl, 3,7-dimethylimidazo[1,2-a]pyridin-2-yl, and 3-chloro-7-methylimidazo[1,2-a]pyridin-2-yl.

4. A process for preparing a compound of the formula :

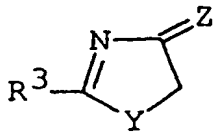


wherein R^1 is heterocyclic group,
X is $(CH_2)_a$ in which a is 0 or 1, O or S,
Y is CH_2, O, S or $N-R^2$
in which R^2 is hydrogen or lower alkyl,
Z is O or H_2, and
m and n are each 0 or 1,
or pharmaceutically acceptable salts thereof,

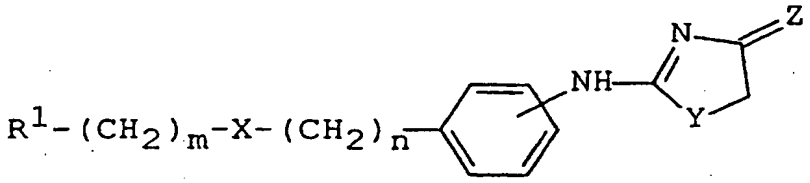
(1) reacting a compound of the formula :



wherein R^1, X, m and n are each as defined above, or a salt thereof, with a compound of the formula :

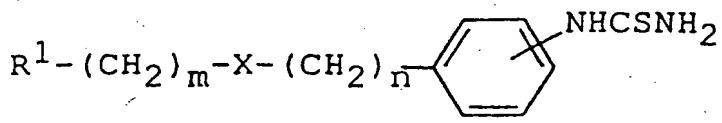


wherein Y and Z are each as defined above, and R^3 is lower alkylthio or halogen, or a salt thereof, to give a compound of the formula :

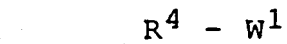


wherein R^1, X, Y, Z, m and n are each as defined above, or a salt thereof, or

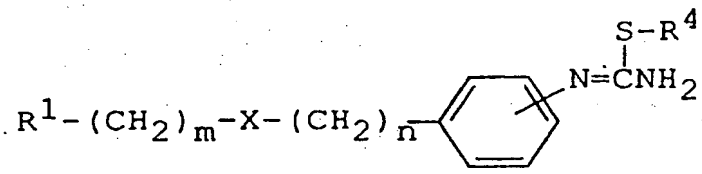
(2) reacting a compound of the formula :



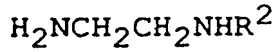
wherein R^1, X, m and n are each as defined above, or a salt thereof, with a compound of the formula :



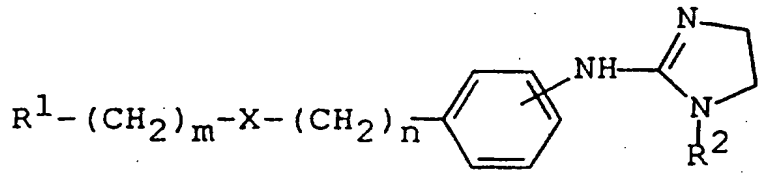
wherein R^4 is lower alkyl, and
W^1 is halogen,
or a salt thereof, to give a compound of the formula :



wherein R^1, R^4, X, m and n are each as defined above, or a salt thereof, and continuously reacting it with a compound of the formula :

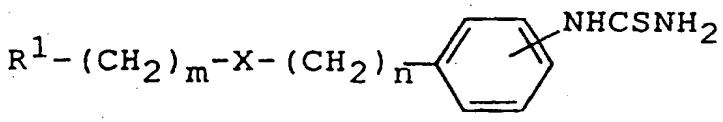


wherein R^2 is as defined above,
or a salt thereof, to give a compound of the formula :



wherein R^1, R^2, X, m and n are each as defined above, or a salt thereof, or

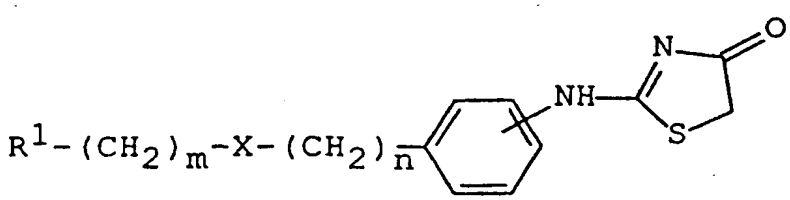
(3) reacting a compound of the formula :



wherein R^1, X, m and n are each as defined above, or a salt thereof, with a compound of the formula :

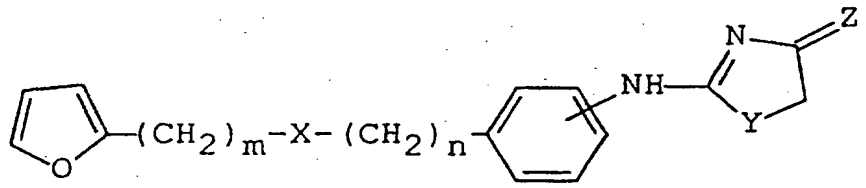
$$W^2CH_2COOR^5$$

wherein R^5 is lower alkyl, and
W^2 is halogen,
or a salt thereof, to give a compound of the formula :

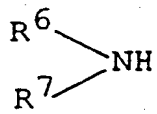


wherein R^1, X, m and n are each as defined above, or a salt thereof, or

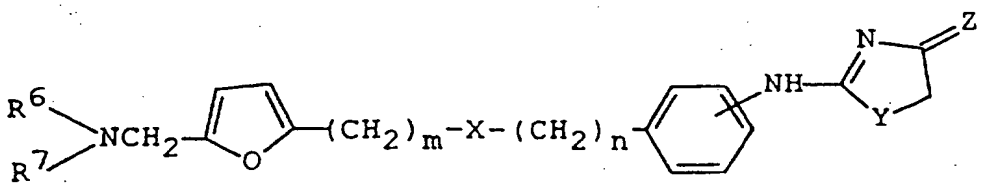
(4) reacting a compound of the formula :



wherein X, Y, Z, m and n are each as defined above, or a salt thereof, with a compound of the formula :



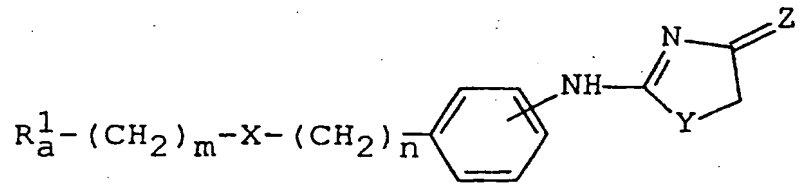
wherein R^6 and R^7 are each lower alkyl, or a salt thereof and with formalin, to give a compound of the formula :



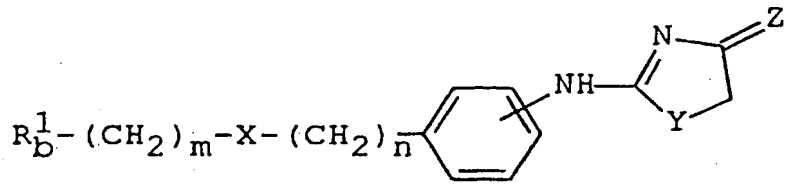
wherein R^6, R^7, X, Y, Z, m and n are each as defined

above,
or a salt thereof, or

(5) subjecting a compound of the formula :

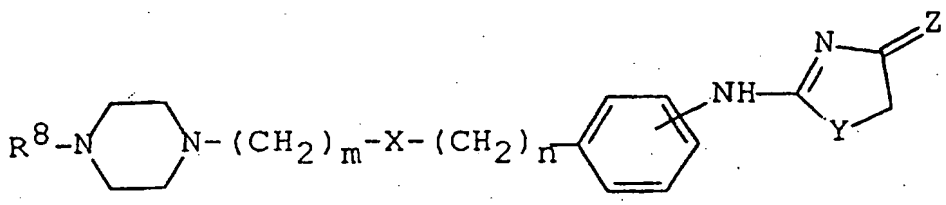


wherein X, Y, Z, m and n are each as defined above, and
R_a^1 is heterocyclic group having acylamino,
or a salt thereof, to deacylation, to give a compound of the formula :



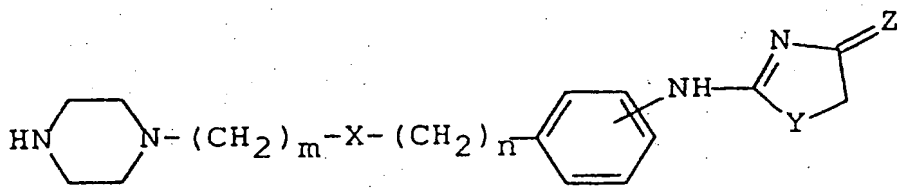
wherein X, Y, Z, m and n are each as defined above, and
R_b^1 is heterocyclic group having amino,
or a salt thereof, or

(6) subjecting a compound of the formula :



wherein X, Y, Z, m and n are each as defined above, and R^8 is acyl,

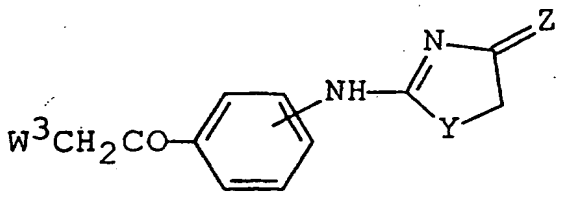
or a salt t thereof, to deacylation, to give a compound of the formula :



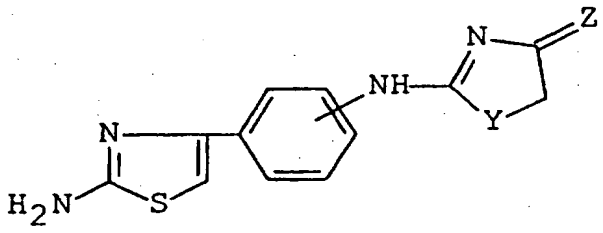
wherein X, Y, Z, m and n are each as defined above,

or a salt thereof, or

(7) reacting a compound of the formula :



wherein Y and Z are each as defined above, and
W^3 is halogen,
or a salt thereof, with thiourea,
to give a compound of the formula :



wherein Y and Z are each as defined above,
or a salt thereof.

5. A pharmaceutical composition which comprises, as an active ingredient, a compound of claim 1 or a pharmaceutically acceptable salt thereof in admixture with pharmaceutically acceptable carriers.

6. A method for the treatment of ulcer which comprises

administering a compound of claim 1 or a pharmaceutically acceptable salt thereof to human or animals.

7. A use of a compound of claim 1 as a medicament.

8. A use of a compound of claim 1 or a pharmaceutically acceptable salt thereof as a medicament for prophylactic and therapeutic treatment of NOS-mediated diseases.

INTERNATIONAL SEARCH REPORT

Inte ›nal Application No
PCT/JP 96/00776

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D277/18 C07D417/12 A61K31/425 C07D471/04 C07D277/40
//(C07D471/04,235:00,221:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,94 12165 (WELLCOME FOUND) 9 June 1994 see claims ---	1-8
A	EP,A,0 279 398 (MERRELL DOW PHARMA) 24 August 1988 ---	
A	US,A,5 066 664 (GLUCHOWSKI CHARLES) 19 November 1991 -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
24 June 1996	- 5. 07. 96
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte onal Application No
PCT/JP 96/00776

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO-A-9412165	09-06-94	AU-B-	5533094	22-06-94
		CN-A-	1095710	30-11-94
		EP-A-	0670720	13-09-95
		JP-T-	8503940	30-04-96
		SI-A-	9300616	30-06-94
		ZA-A-	9308867	26-05-95
EP-A-0279398	24-08-88	US-A-	4788209	29-11-88
		DE-A-	3869156	23-04-92
		JP-A-	63264469	01-11-88
US-A-5066664	19-11-91	NONE		